Childhood Onset Schizophrenia (COS): update 2017

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Demystifying Medicine

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Childhood Onset Schizophrenia: update

- Disclosures: none

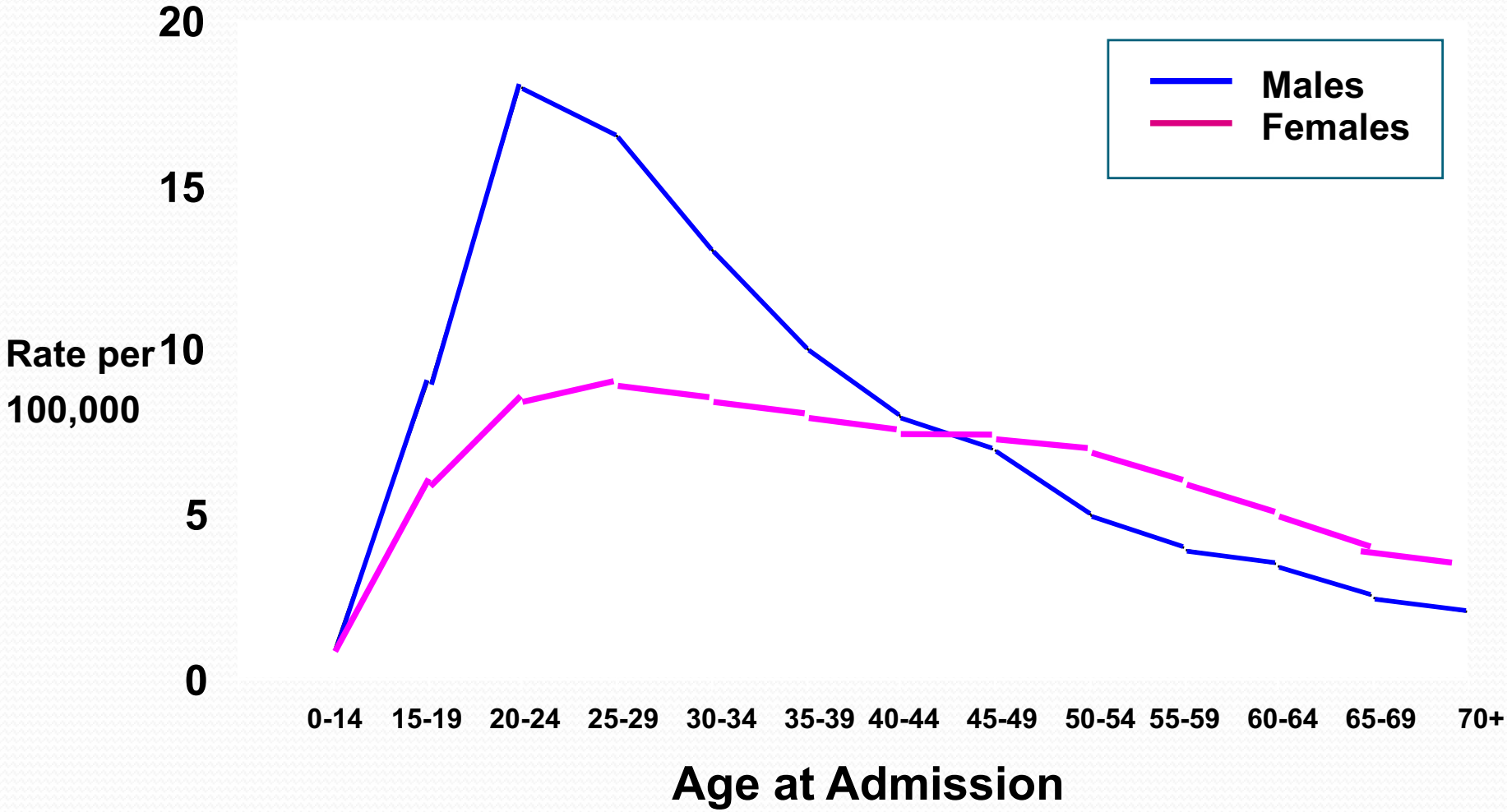
- Objectives:
- 1) To identify salient clinical and neurobiological features of childhood onset psychosis
- 2)Update on on brain development/function in COS
- 3) Genetic risk in COS & CNV risk within a clinical pediatric population

Schizophrenia: DSMV

- Two or more: hallucinations, delusions, disorganized speech, disorganized behavior, negative symptoms (e.g. decreased emotional expression)
- Decreased Functioning: e.g. in work, personal, self care, personal relations
- Duration at least six months
- Other disorders (e.g. bipolar) ruled out
- If history of autism spectrum disorder, must have hallucinations and/or delusions

First-Admission Rates for Schizophrenia per 100,000 Population by Sex

(Admissions in the UK in 1984)



Castle & Murray, 1993

- CHILDHOOD ONSET SCHIZOHRENIA: PATIENT “A”
- Described as having a “normal, happy childhood” till age 9.
- By age 10, bizarre behavior included public masturbation, refusing to go to bed due to fear of bugs, and aggression, leading to 4 psychiatric hospitalizations for: aggression, delusions (mermaid in head controlling her thoughts), hallucinations and inappropriate affect.
- Discharged after a 10 month inpatient stay. protocol, having been tried on Mellaril, Navane, Stelazine, Prolixin, Lithium.
- Age 14 entered NIH childhood onset schizophrenia study
- She was discharged from NIH on Clozapine to a state hospital more organized with less frequent delusions and hallucinations.
- Six years later, found to have been continuously hospitalized. Maintained on clozapine.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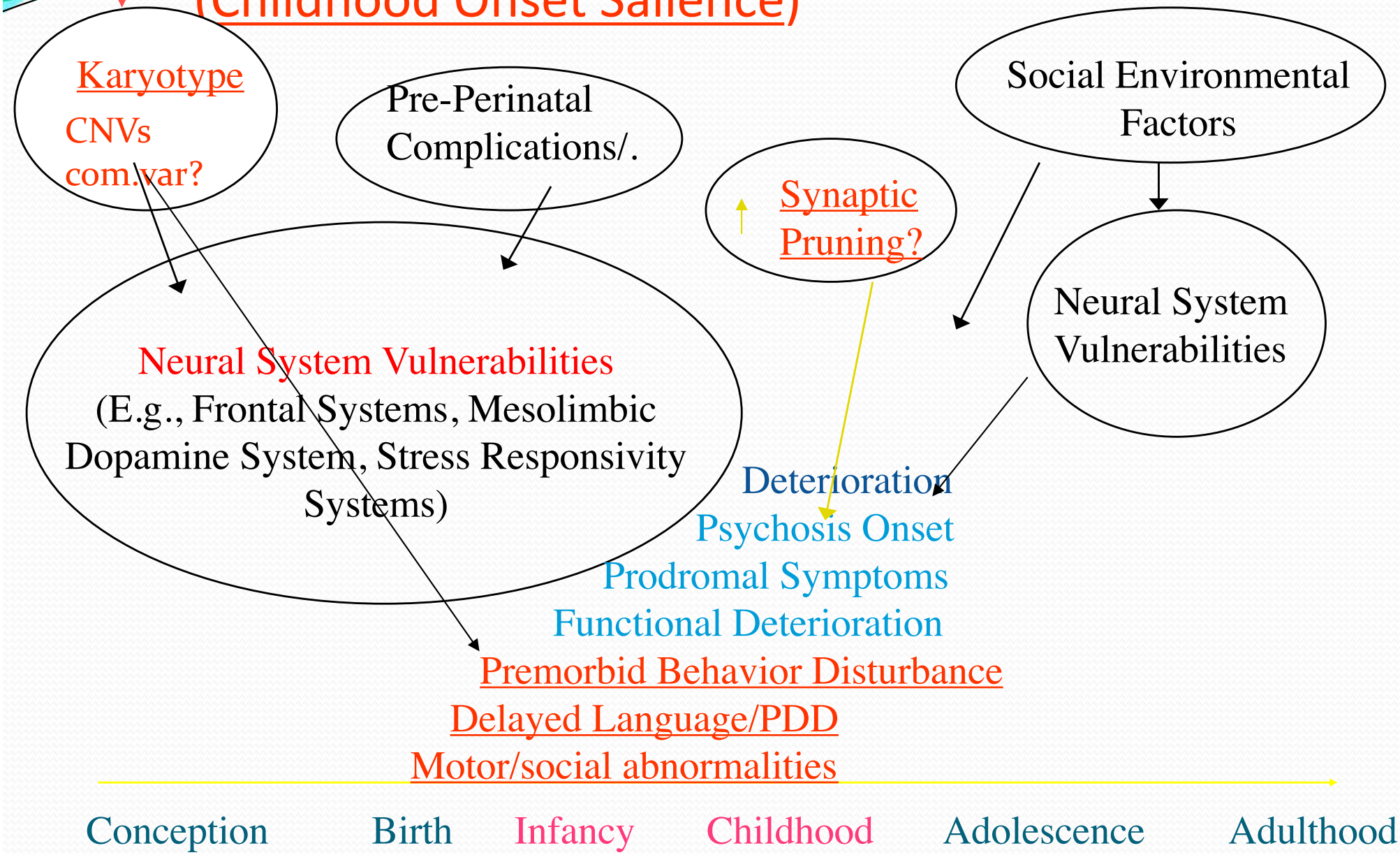
Schizophrenia:Theoretical Framework (Childhood Onset Salience)



Previous clinical studies

Risk: *no* strong indication of special salience for COS :

- Obstetrical risk (obstetrical record comparison vs. siblings)
- Early puberty
- Paternal age
- Season of birth
- Trauma
- Sibling neuro-developmental impairment

Continuity with AOS

- Unmodified DSM IV Diagnosis
- Neuropsych Profile
- Skin conductance
- SPEM
- Anatomic brain MRI (e..increased ventricular and decreased GM & hippocampal volumes)Resting state fMRI similar to adult pts

Treatment

- Double blind superiority of clozapine vs haloperidol
- Double blind superiority of clozapine vs olanzapine
- 72% long-term clozapine compliance
- Safety study of TDCS

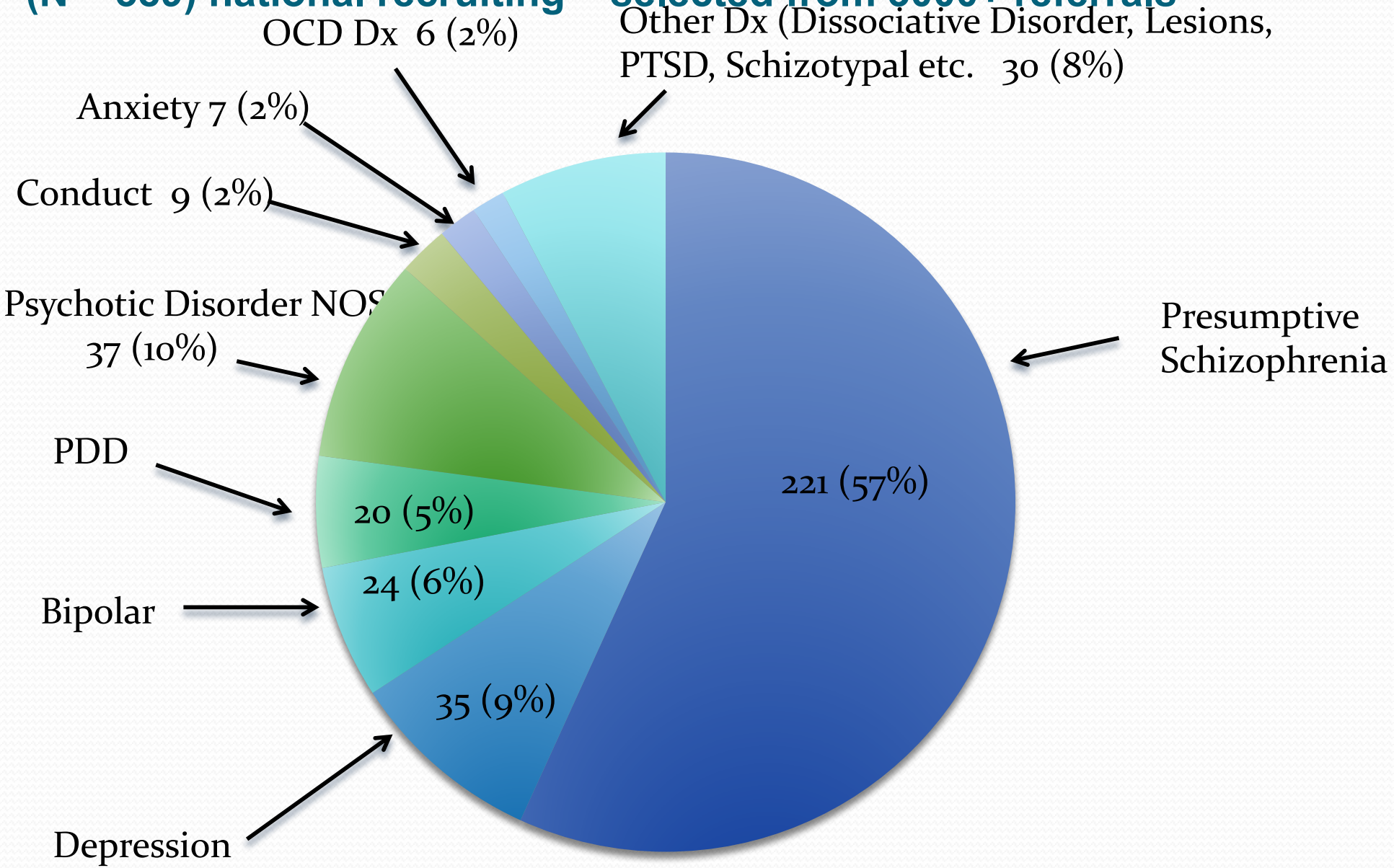
Childhood Onset Schizophrenia: rare but worth studying

I. **Phenomenology: resembles poor outcome adult onset patients with insidious onset, marked pre- psychotic neurodevelopmental impairments. Marked non specificity of premorbid disorder suggests widespread commonabnormalities in brain developmental processes**

II. Brain Imaging: more severe GM deficit in probands **Early** -timing rather than volume abnormalities dysconnectivity, abnormal resting state pattern comparison with AOS,

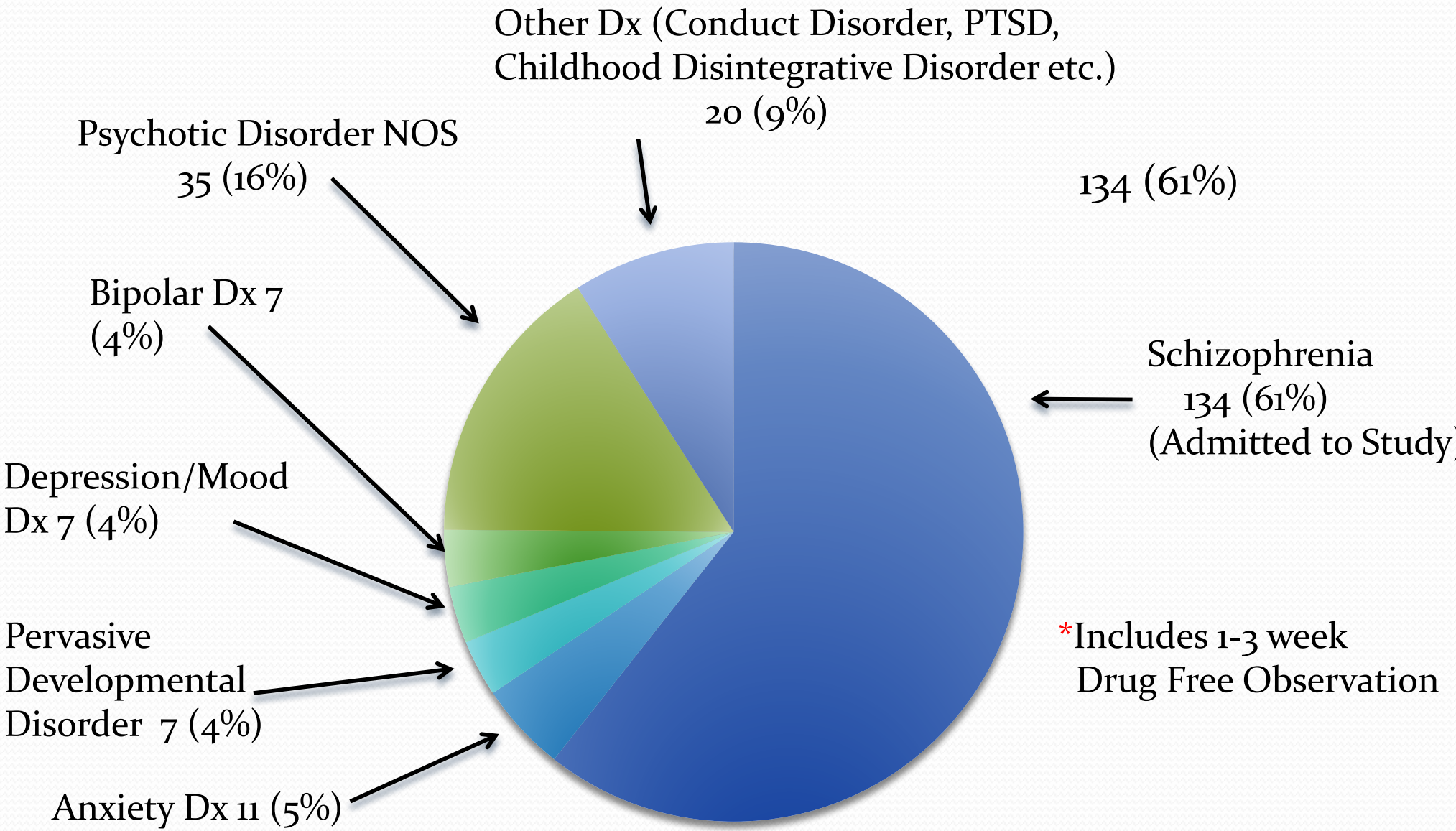
III. Genetics: High Rate of Copy Number Variants COS > AOS; non-specificity & heterogeneity of genetic risk. Extension – CNV based and sequencing studies CHOP study shows non specificity of risk

Over-diagnosis of Childhood-Onset Schizophrenia:
Primary Diagnosis after initial Two-day Out-Patient Screenings
(N = 389) national recruiting – selected from 3000+ referrals



March, 20167

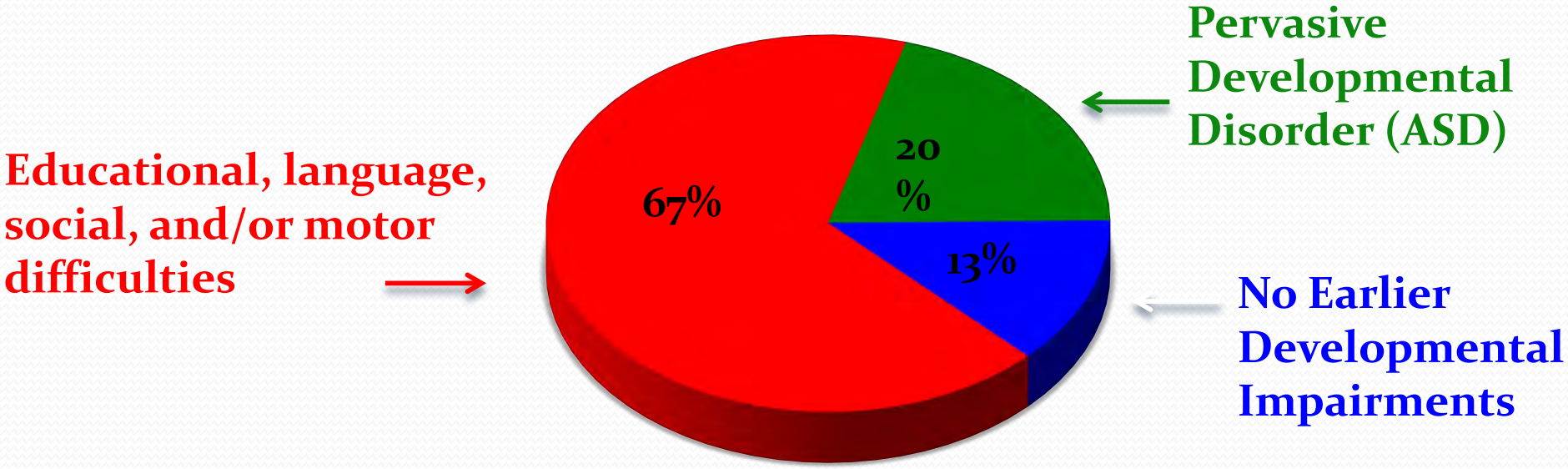
Childhood-Onset Schizophrenia: Discharge Diagnosis after 221 In-Patient Admissions March, 2017*



Sample Demographics: COS, COS Siblings and COS Parents (March, 2016)

	COS	***COS Parents***	***COS Siblings***
Subject Number	135	251	163
Age of Onset	9.9 +/- 2.0	N/A	N/A
Years ill (Probands)	3.2 +/- 3.4	N/A	N/A
Age at 1st contact	**13.1 +/- 2.5**	44.3 +/- 6.7	13.7 +/- 6.3
Gender (Males)	73 (54%)	123 (49%)	79 (48%)
Ethnicity	-	-	-
Caucasion	73 (54%)	125 (50%)	98 (60%)
African American	41 (30%)	73 (29%)	31 (19%)
Hispanic	17 (13%)	22 (9%)	14 (9%)
Asian	6 (4%)	13 (5%)	7 (4%)
Other	10 (7%)	18 (7%)	13 (8%)
Parental SES	2.5 +/- 1.8		
Full Scale IQ (Highest)	82.5 +/- 18.2	N/A	N/A
Age at first evaluation for Neurodevelopmental problems	6.2 +/- 2.5	N/A	N/A

High Rates of Pre-Psychotic Neurodevelopmental Impairment for Childhood Onset Schizophrenia Probands (March, 2017)



Genetic/familial risk? Not high rate of sibling neurodevelopmental impairment
Comorbidity? Many improved or remitted by onset of psychosis
Earlier manifestation of illness? Non-specific/common/diffuse as measureable from history and medical and medical records. M>F for ADHD and PDD comorbidity but high overall rates.

Childhood Onset Schizophrenia: rare but worth studying

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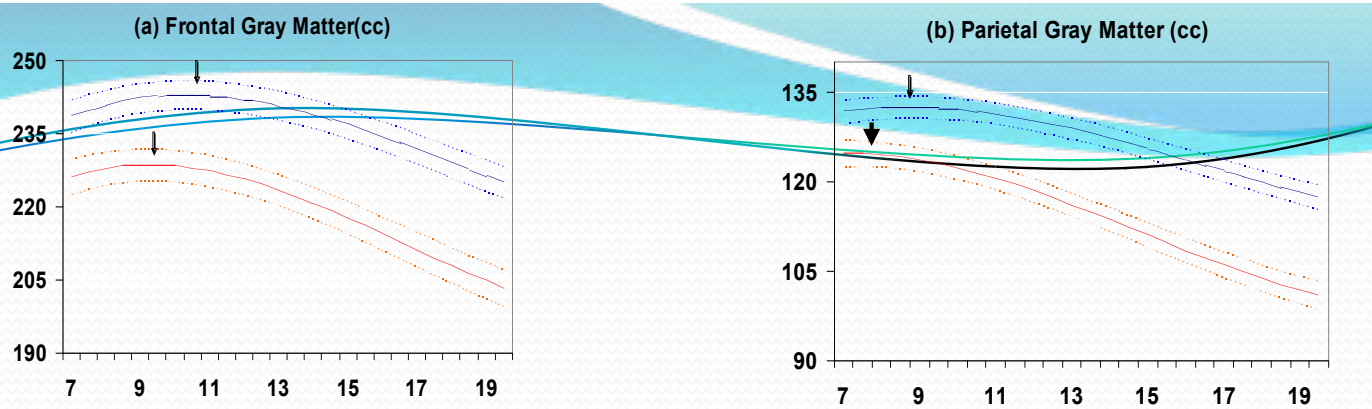
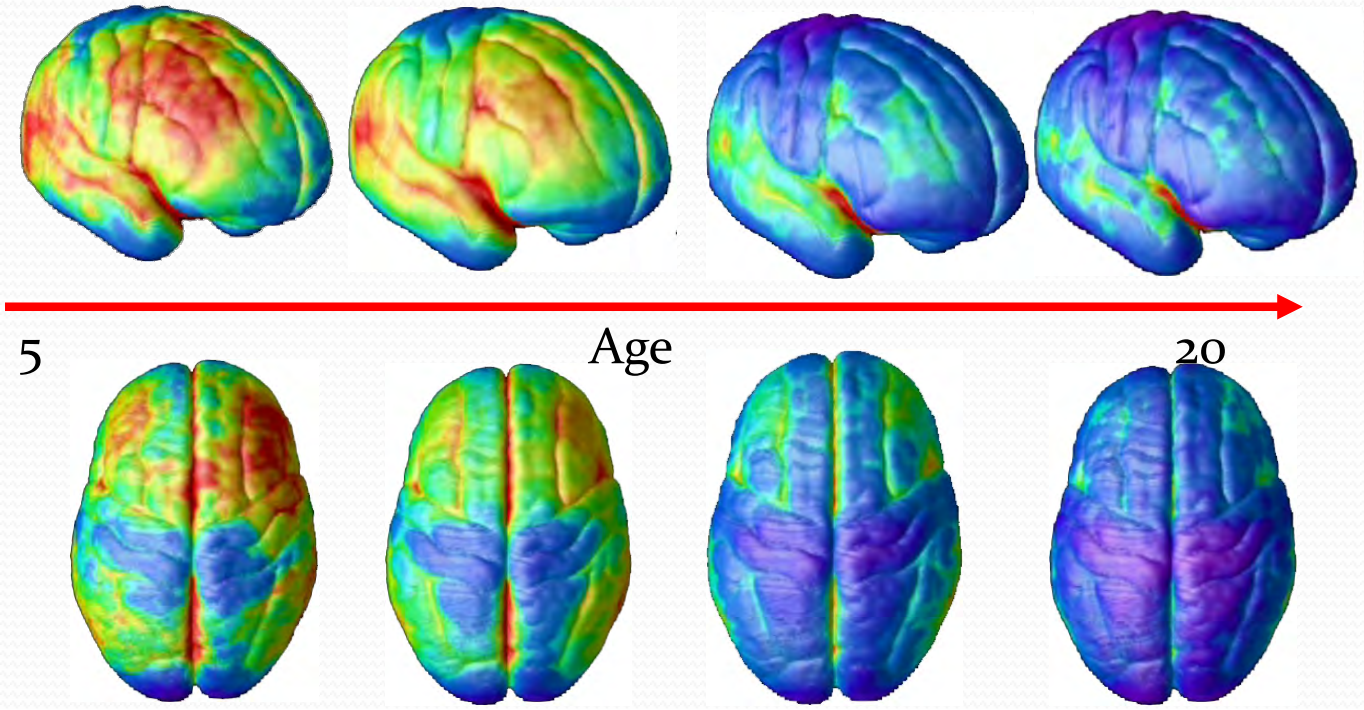
Extension – treatment studies: (oxytocin & TDCS)

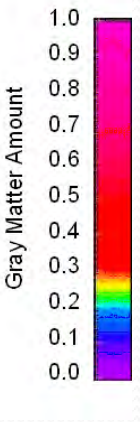
II. Brain Imaging: anatomic -more severe GM deficit in probands
Early GM deficits in siblings; -timing rather than volume
Extension: fMRI imaging of probands and siblings – age related dysconnectivity, abnormal activation pattern,

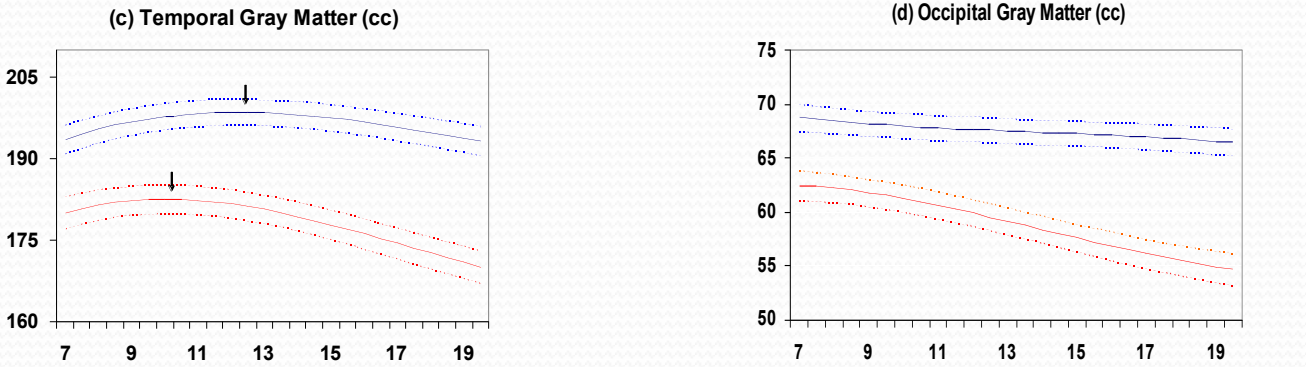
III. Genetics: High Rate of sex chromosome and other chromosomal abnormalities
High rate of Copy Number Variants COS > AOS; high rate in Alternate Diagnosis group. Non-specificity & heterogeneity of genetic risk. Higher polygenetic score?
Extension – CNV based screening to assess clinical burden, iPSC , sequencing studies
Pediatric Population study CNV- to Phenotype

Figure 1



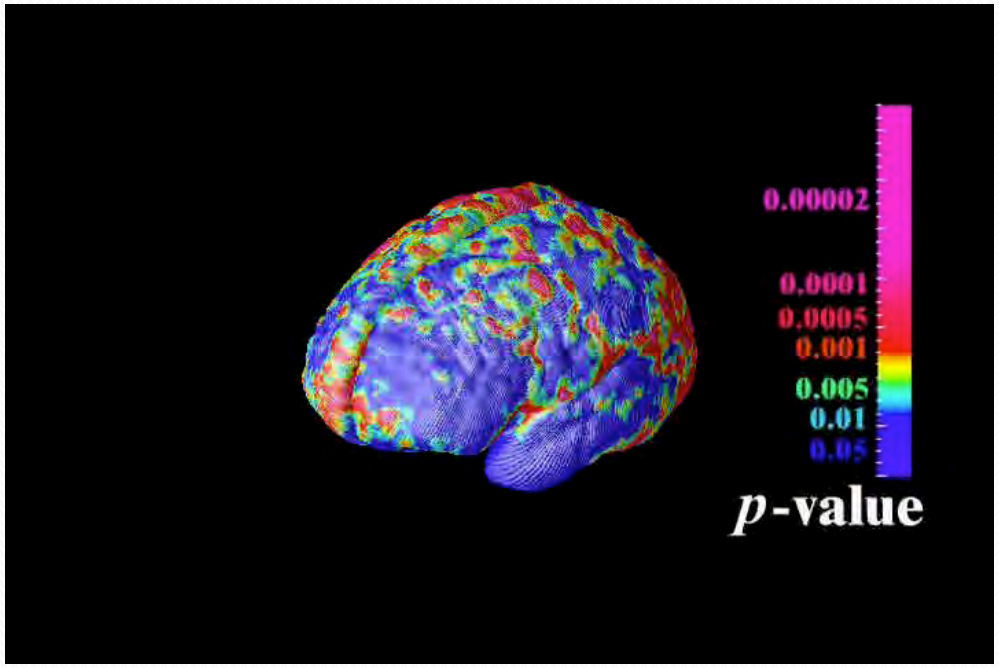






Adapted from Gogtay et al. 2004 Giedd et al. 1999

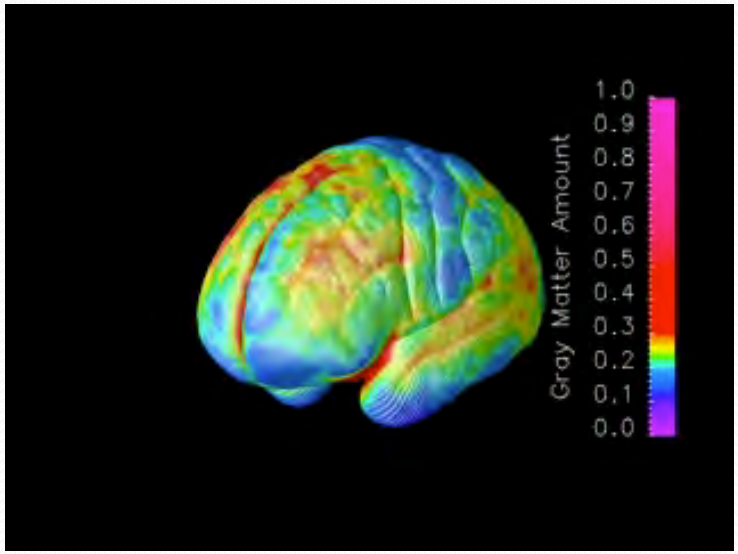
COS Brain Development
Age 12-16



COS n=12 Vs Controls n=12; 3 scans each
Age, sex and scan interval matched.

Thompson et al.
PNAS 2001

~~Normal~~ Brain Development
Age 4-22



n=13; 51 scans

Gogtay et al. PNAS
2004

COS HAS EXAGGERATED PATTERN OF NORMAL CORTICAL DEVELOPMENT

Whole-Brain Functional Connectivity in COS

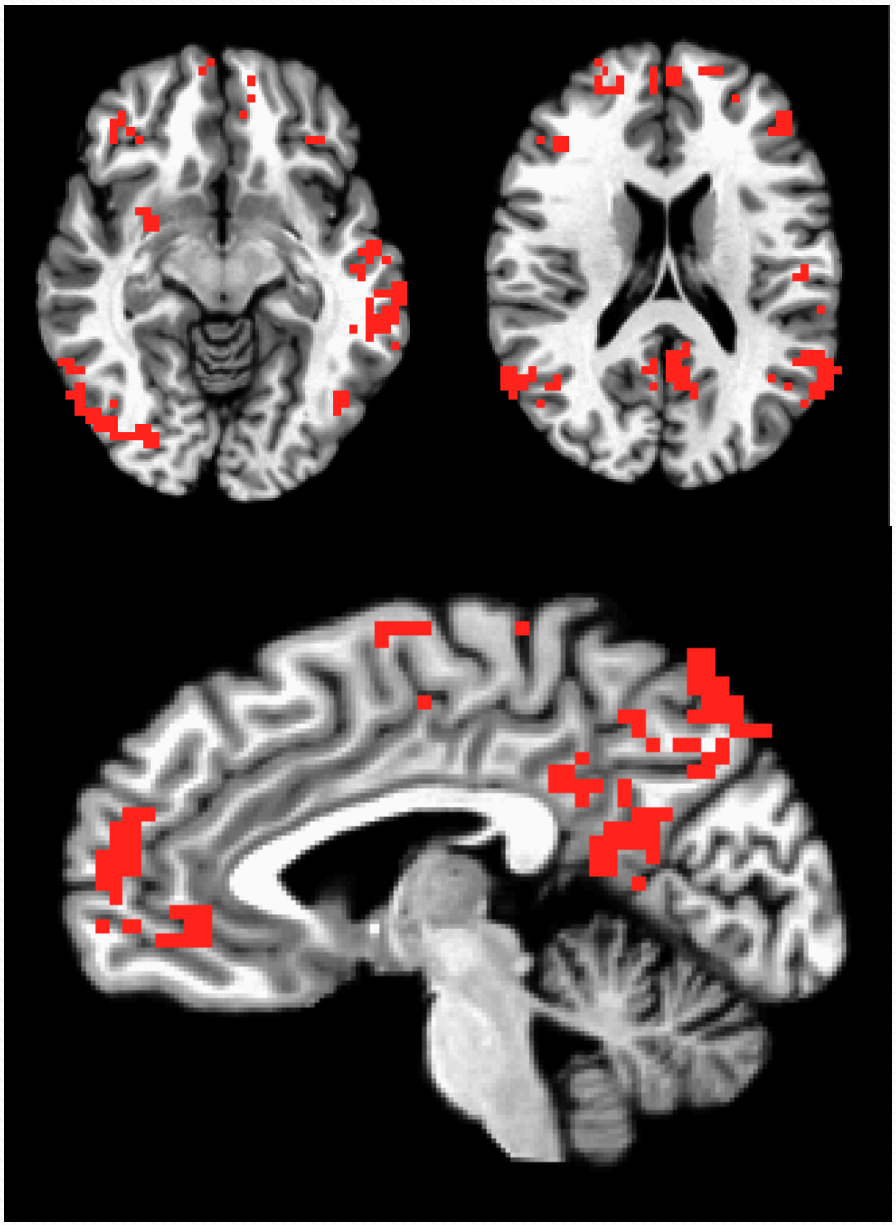
Our sample: 19 COS patients and 26 age-, sex-, and handedness-matched normal volunteers, eyes open resting-state

We used methodology pioneered by Gotts et al 2012 to identify 26 regions with aberrant connectivity in the COS brain

- Whole-brain
- Agnostic, data-driven
- Cleaner removal of physiological noise
- Results that are organized and correlate with clinical measures

We then asked:

1. Do these regions represent distinct functional networks?
2. How do the networks differ for COS compared to controls?
3. How do clinical measures map onto group differences?



Cluster analysis of the 26 regions revealed two functional networks

Region of Interest	x	y	z
Right Medial Prefrontal	6	57	7
Left Medial Prefrontal	-4	55	8
Right Superior Frontal / BA 10	22	49	16
Right Inferior Frontal	51	31	8
Left Inferior Frontal	-43	37	9
Right DLPFC	27	17	43
Left DLPFC	-25	18	46
Right Middle Temporal	58	-54	13
Left Middle Temporal	-54	-55	12
Right Fusiform / IT	56	-54	-13
Left Fusiform / IT	-51	-54	-13
Right Posterior Cingulate	6	-55	25
Left Posterior Cingulate	-4	-56	21
Right IPL/Angular Gyrus	32	-67	36
Left IPL/Angular Gyrus	-36	-65	35
Right Precentral Gyrus	45	-6	46
Left Precentral Gyrus	-38	-11	43
Right Putamen	29	-8	6
Left Putamen	-26	-10	6
Left SMA	-8	-8	64
Right Middle Frontal	20	-16	60
Left Superior Temporal	-48	-19	6
Left S2	-13	-29	44
Left Postcentral Gyrus	-9	-38	64
Right Inferior Cerebellum	19	-56	-43
Left Inferior Cerebellum	-19	-55	-44

RED CLUSTER

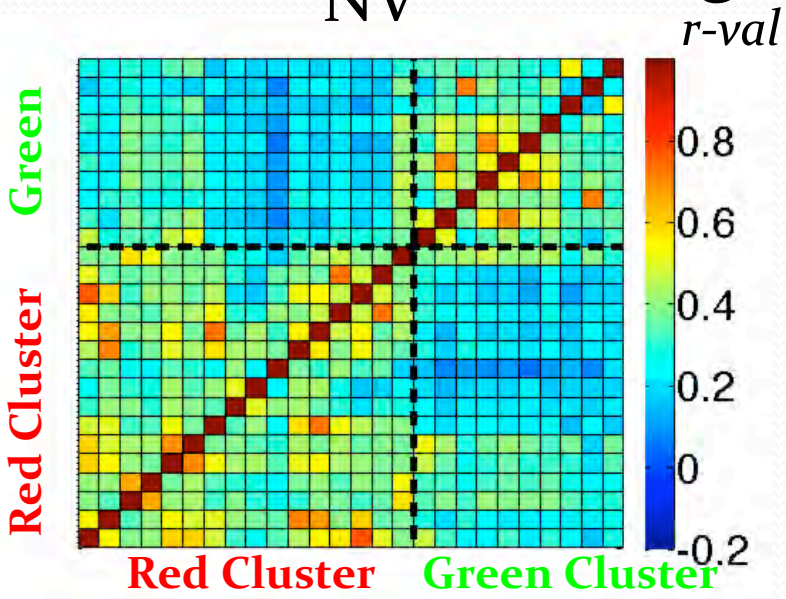
Heteromodal, high-level association areas, social brain regions

GREEN CLUSTER

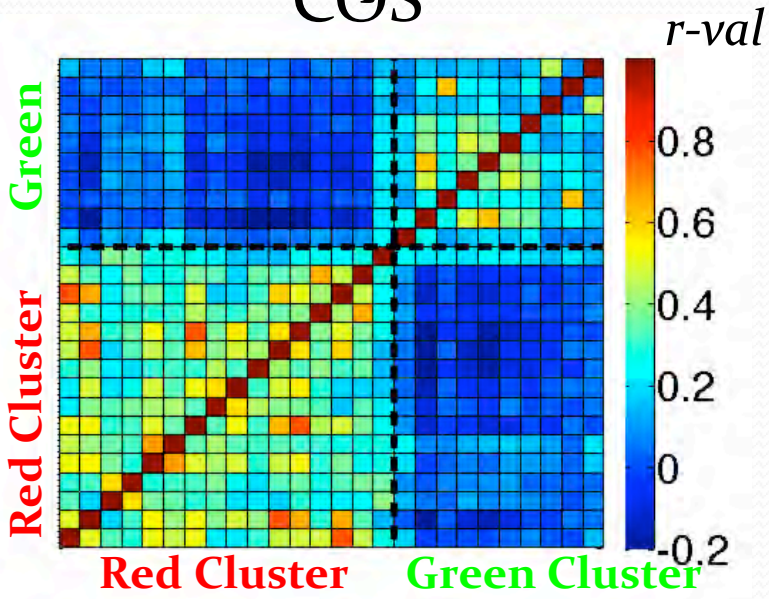
Somatosensory/motor brain areas

COS patients show decreased across-network Resting-state connectivity

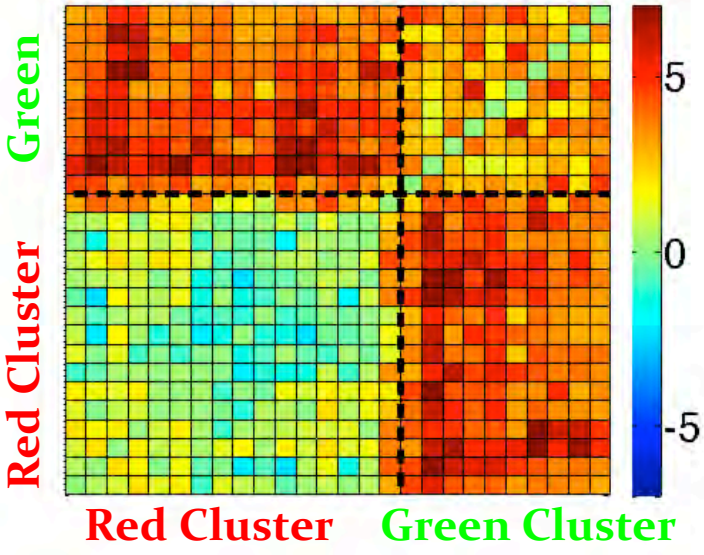
NV



COS



NV - COS



t-val
(df = 43)

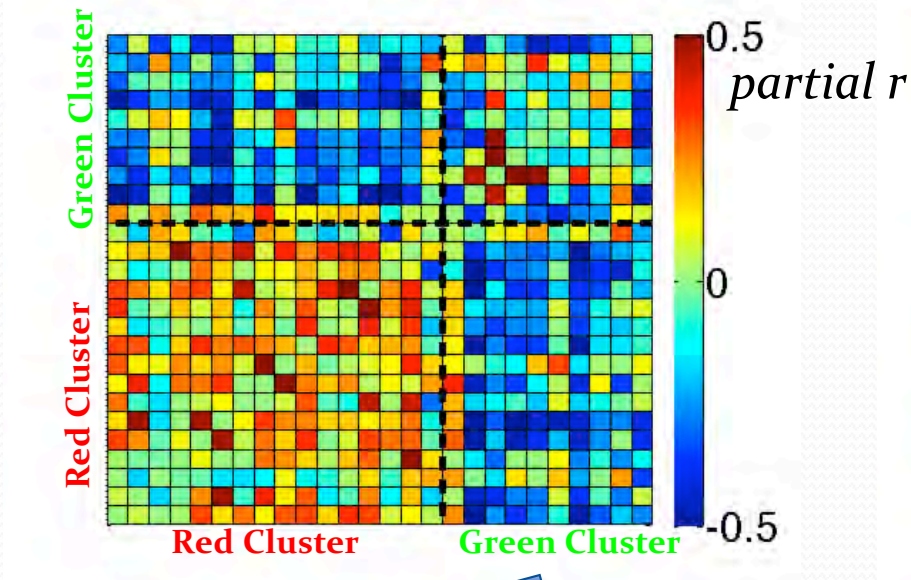
Red = Heteromodal, high-level association areas, social brain regions

Green = Somato-Sensory, Motor Brain areas

Berman et al Brain:2015

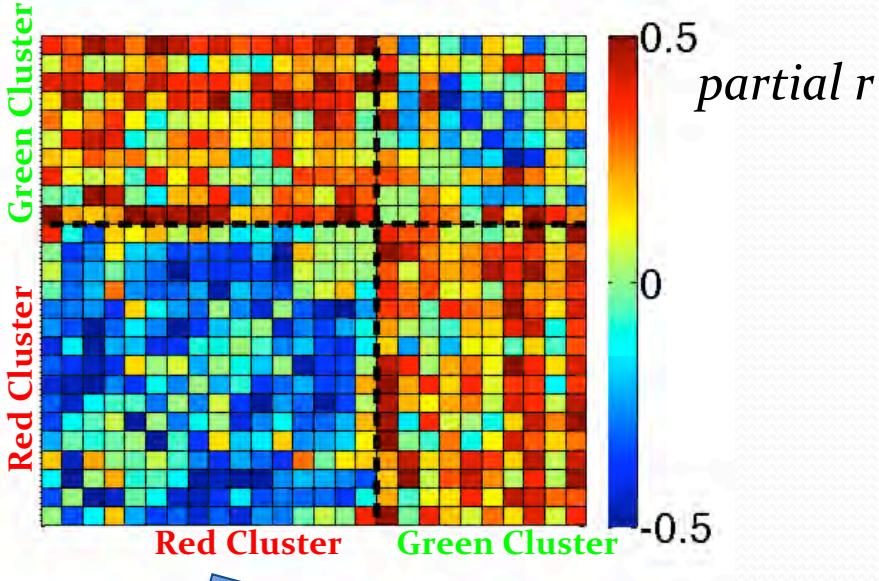
Region-by-region connectivity correlates with symptoms, in a pattern consistent with observed network structure

Correlation with SAPS
(covarying Age, Motion, Cloz Dose)



Reduced across-network connectivity is associated with more positive symptoms

Correlation with SANS
(covarying Age, Motion, Cloz Dose)



Reduced connectivity within the social-brain network is associated with more negative symptoms

Berman et al Brain, 2015

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Pediatric Population study CNV- to Phenotype

Cytogenetic risk in COS and Alternate Disorder Patients

	COS probands (n=136)	**AD patients (n=87)**
Neurodevelopmental disorder associated CNVs	20 (14.7%)	11 (12.6%)
Chromosomal abnormality	5 (3.8%) • 46,X,del(X)(q24-ter) • 78% XO; 22% idicXq • Trisomy X • 1;7 balanced translocation • 5q32-ter uniparental isodisomy	4 (4.6%) • XYY • XXY • XYY • XXY
Sequence mutations	1 (0.8%) • UPF3B frameshift	1 (1.1%) • SHANK3 de novo missense
Total	26 (19.1%)	16 (18.4%)

42 out of 223 patients: 18.8%

Selection of Disease-related CNVs for COS study:

1. Previously published studies that had focused on: Autism, Schizophrenia, Intellectual disability, and/or Epilepsy
2. Study Sample size of cases or probands > 300 (range of sample size, 400~24,000

A total of 25 studies (9 schizophrenia, 8 autism, 5 ID and 3 epilepsy) met these criteria.

3. **Based on these 25 studies, 46 loci were chosen**

Confirmation of disease-related CNV:

1. **Size >100kb**
2. **Interrupting at least 1 gene**
3. **CNV within or overlapping 50% of a disease related locus**

•

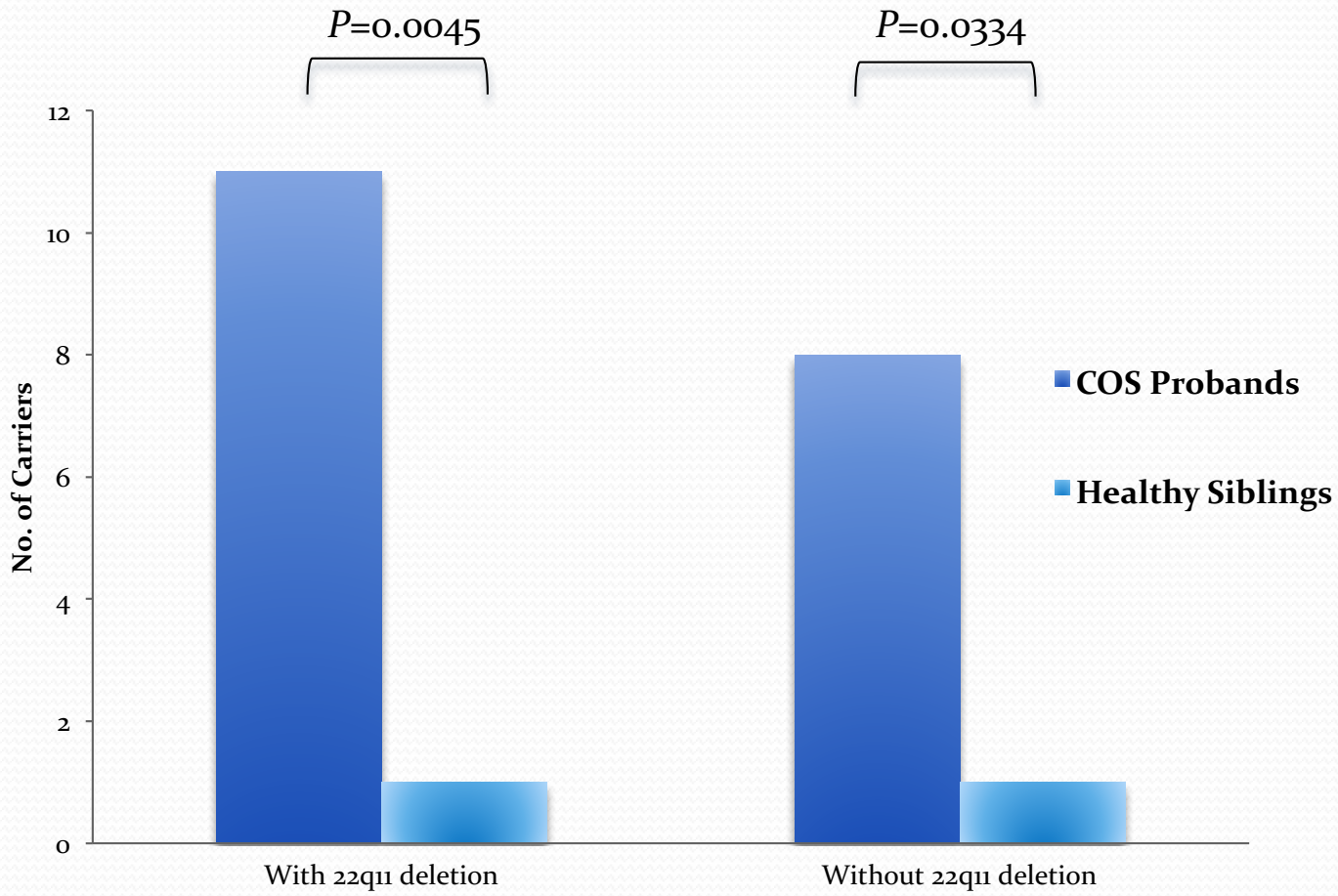
15% of 136 COS patients carry neuro-developmental risk CNVs (as of 3/16)

NSB ID	Chr Band	Start (hg18)	Stop (hg18)	size (kb)	Type	Duplicated or Deted genes	Inheritance	Disease
3207	1q21.1	146,089,268	147,706,692	1,617.4	Dup	4	Father	SCZ, ID
3127	1q21.1	145,629,767	146,039,634	409,9	Dup	3	Mother	SCZ, ID
885	1q21.3	151,508,301	151,773,800	265.5	Dup	9	Father	SCZ, ID
581	2p16.3	50,025,162	50,136,989	111.8	Del	2	na	SCZ, ASD
1358*	2p25.3	1,591,064	1,836,375	245.3	Dup	2	Mother	SCZ
534*	2p25.3	1,720,133	1,827,317	107.2	Dup	2	na	SCZ
534*	8q11.2	53,550,992	54,043,684	493	Dup	3	Unknown	ID
885	10q22.3	81,415,378	81,588,866	173.5	Del	5	*de novo*	ID
3261	15q11.2	20,889,274	21,157,642	268.4	Dup	7	Mother	SCZ, ID, Epi
1358*	15q11.2	20,203,694	20,778,963	575.3	Del	13	Mother	SCZ, ID, Epi
448	15q11.2	18,818,086	20,203,694	1,386	Del	24	na	SCZ, ID, Epi
3248	15q13.3	32,012,361	32,515,849	503.5	Dup		father	SCZ, ID, Epi, ASD
1546*	15q13.3	30,238,780	30,620,951	382.2	Del	26	*de novo*	SCZ, ID, Epi, ASD
498	15q13.3	30,238,780	30,713,368	474.6	Del	30	Mother	SCZ, ID, Epi, ASD
2011	16p11.2	29,782,436	30,227,808	445.4	Dup	34	Father	SCZ, ID, Epi, ASD
676*	16p11.2	29,502,984	30,107,306	604.3	Dup	15	Unknown	SCZ, ID, Epi, ASD
481	16p12.1	21,498,074	21,946,841	448.8	Del	7	Father	ID
1546*	17q21.31	41,521,621	41,706,070	184.4	Dup	2	Father	ID
3228	22q11.21	18,882,185	21,608,479	2,726.3	Del	44	*de novo*	SCZ, ASD, ID
3169	22q11.21	17,269,794	20,128,199	2,858.4	Del	55	*de novo*	SCZ, ASD, ID
1804	22q11.21	17,257,787	19,963,350	2,705.6	Del	47	*de novo*	SCZ, ASD, ID
1275	22q11.21	17,092,563	20,077,678	2,985.1	Del	89	*de novo*	SCZ, ASD, ID
1220	22q11.21	17,224,632	19,842,333	2,617.7	Del	48	*de novo*	SCZ, ASD, ID
537	22q11.21	17,257,787	19,855,248	2,597.5	Del	46	Unknown	SCZ, ASD, ID
676*	22q13.33	49,403,228	49,557,485	154.3	Dup	1	*de novo*	ASD

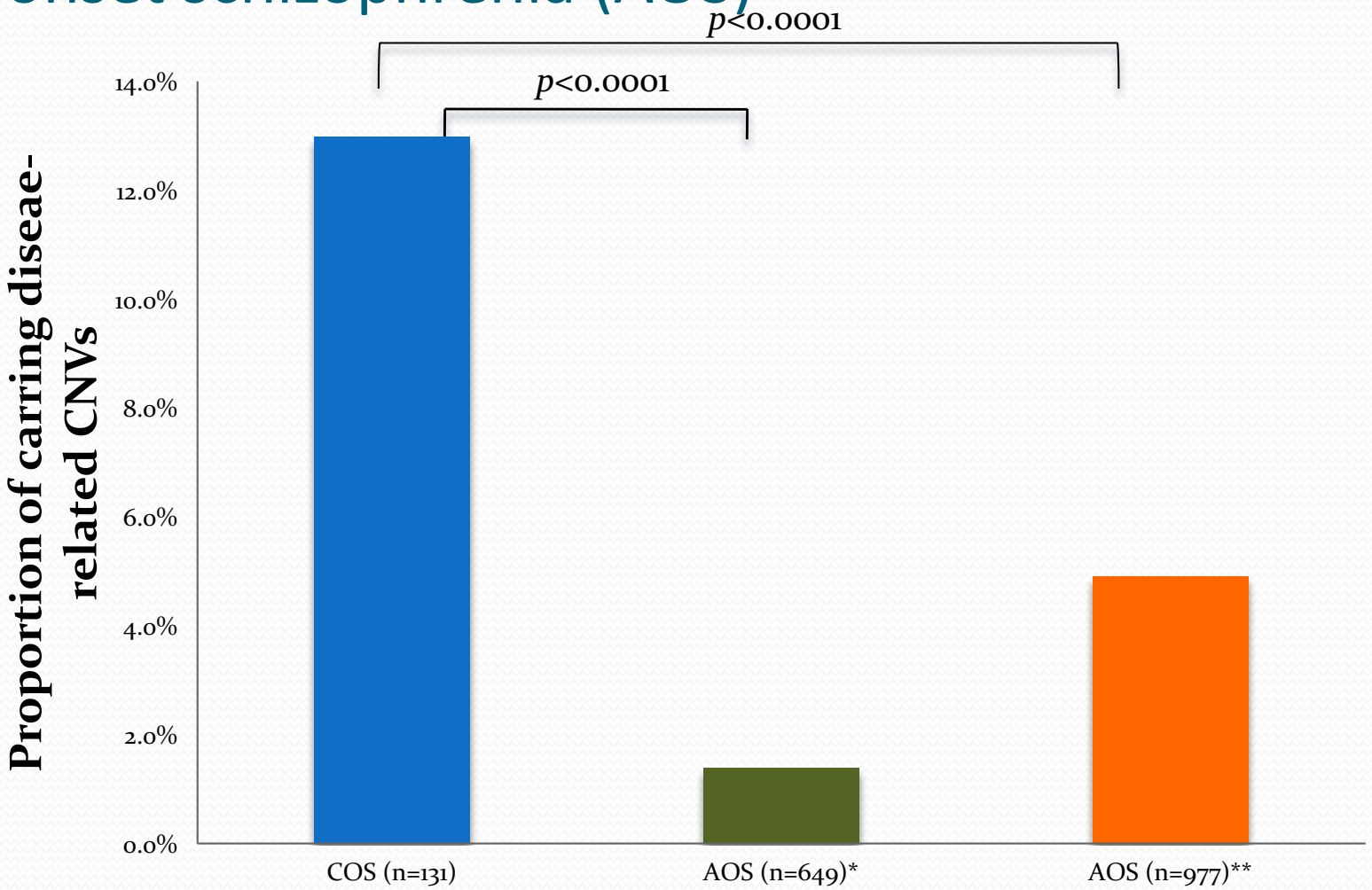
Abbreviations: ASD, autism spectrum disorders; COS, childhood onset schizophrenia; CNV, copy number variants; Epi, epilepsy; ID, intellectual disability; SCZ, schizophrenia. * Individuals with two events

N=136

Carrier Status of COS proband-Healthy sibling Pairs (n=73)



Rates of selected Neurodevelopmental disorder-related CNVs in Childhood onset schizophrenia (COS) vs Adult onset schizophrenia (AOS)



* Samples in Guha *et al.* (2013)

** Samples in Glessner *et al.* (2010)

Discharge Diagnoses in 87 "Alternate Diagnosis" Patients (all severe, very early onset; differentiated from COS after inpatient observation. Screened for 46 "neurodevelopmental "CNVs

Primary Diagnosis	N
Bipolar	7
Schizoaffective-depressed	3
Autism Spectrum Disorder	7
Psychosis NOS	35
ADHD	11
Anxiety	11
Mood Disorder	7
Other*	6
Total	87

*OCD (1), ODD (1), Childhood Disintegrative Disorder (1), Learning Disorder NOS (1), Personality Disorder NOS (1), Schizotypal Personality Disorder (1)

11/87 (12.6%) patients receiving Alternate Diagnoses also carry neurodevelopmental disorder associated CNVs (i.e.non-specific risk)

NSB	DX	Chr Band	Type	Genes	Inherited	Disease	Rate in control	p
3127	Psychotic Disorder NOS/ ADHD/ ODD/Sep Anxiety	1q21.1	dup	4	mother	SCZ, ASD and ID	3/10,910	0.0070
973	Psychotic Dis NOS/ADHD	2p16.3	del	NRXN1	mother	SCZ	10/45,184	0.0006
2885	ASD/ADHD	7q36.3	dup	VIPR2	father	SCZ	2/3,611	0.0007
774	ASD/ Epilepsy	15q11.2	dup	7	father	SCZ, Epi	40/10,209	0.3029
852	Psychosis NOS/Maj Dep with psychotic features	15q13.3	dup	7	father	SCZ, ASD, ID and Epi	4/10,529	<0.0001
2516	OCD/ADHD/lang disorder	16p13.1	dup	12	mother	SCZ, ASD, ID and Epi	38/37,871	0.0036
2564	ASD/Maj Dep with psychotic features	16p13.1	del	16	father	SCZ, ASD, ID and Epi	1/4,329	<0.0001
521	Motor Tic Disorder	16p12.1	dup	12	Na	ID	3/8,329	<0.0001
510	Psychotic Dis NOS/Panic Dis/pedophilia	16p11.2	dup	45	mother	SCZ, ASD	8/28,403	<0.0001
686	ASD/Psychotic Dis NOS /GAD/ADHD	17p12	del	11	mother	SCZ, ASD	6/38,884	<0.0001
3253	ADHD/Personality Disorder NOS/ Dyslexia	17q21.3	dup	7	mother	SCZ, ASD, ID	0/8329	0.0103

What about common variants?Polygenetic Scores for Childhood Onset Schizophrenia Patients and Their Healthy (non psychotic) Siblings

Table 3. Thresholds, number of SNPs for polygenic score and summary of results in the comparison of COS probands (N=130) and Healthy siblings (N=103)

Discovery data	*Threshold*	*Selected SNPs*, n	P (COS vs SIBS)	R^2
PGC-SCZ	$P_T = 0.1$	13 717	< 0.0001	0.0668
PGC-SCZ	$P_T = 0.2$	22 968	< 0.0001	0.1030
PGC-SCZ	$P_T = 0.4$	37 402	< 0.00001	0.1852
PGC-ASD	$P_T = 0.1$	8688	0.3062	3.6E − 05
PGC-ASD	$P_T = 0.2$	17 404	0.1294	0.0002
PGC-ASD	$P_T = 0.4$	34 662	0.0150	0.0648

Abbreviations: COS, childhood-onset schizophrenia; PGC-ASD, autism GWAS in Psychiatric Genetics Consortium; PGC-SCZ, schizophrenia GWAS in Psychiatric Genetics Consortium; SNPs, single nucleotide polymorphisms.

Summary: common variants

- Polygenic risk score for schizophrenia significantly predicted COS status.
- First demonstration of significant overlap in polygenic susceptibility to autism and early-onset schizophrenia.
- The estimated variances using R^2 based on the schizophrenia risk variants in this sample (range 5.5 ~ 18.5%) are stronger than that for the polygenic score representing later-onset schizophrenia (~6%) or bipolar disorder (~3%).
- COS patients may have a more salient genetic risk with respect to common variants than do adult-onset patients.
- Note: Very rare subgroup so precluded replication

Summary of Childhood Onset Schizophrenia Study

- More striking pre morbid neurodevelopmental disorders including PDD
- Greatly over-diagnosed
- More striking severe chronic disorder
- Biological Measures – MRI brain development and Rare and Common variants more striking than for adult onset disorder
- For those not responding to other antipsychotics clozapine should be tried with careful monitoring

From Copy number Variant to Phenotype: a Pediatric Clinical Population Study

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Of 11 different CNVs found more frequent in the COS sample than in controls, 5 also overrepresented compared to AOS

CNV	Rate in COS cases	Rate in AOS cases	P-value	Reference
2p16.3 del[a]	1/131	23/12,627	0.1605	Levinson et al. (2011)
2q25.3 dup	2/131	7/ 5,233	0.0024	Vrijenhoek et al. (2008) Lee et al. (2012)
15q13.3 del	2/131	21/10,887	0.0052	Grozeva et al. (2012)
16p11.2 dup	2/131	26/8,590	0.0274	Grozeva et al. (2012)
22q11.2 del	56/131	35/11,400	<0.0001	Grozeva et al. (2012)

[a] the COS group tended to have higher rate than AOS group with Odds Ratio, 4.2

Collaborative CNV based study with CHOP to examine these four CNVs in pediatric population study of 100,0000: goals to assess overall clinical burden, and define broader neuro-developmental phenotypes. Ability to re-contact subjects (Drs. Hakonarson & Gur).

Initial Hypotheses

- Schizophrenia associated CNVs would have striking relative penetrance for other DDs in a pediatric population

- CNV carriers would have even greater broadly defined penetrance for disorders across disease categories in pediatric population

- Psychiatric in person follow-up (if feasible) will further broaden the CNV related phenotype across DSM categories

Strategy

- Genome First, then Phenotypes
- Broad concept of penetrance
- sum of significant disorders/cost
- Pediatric population medical records

Population for the CHOP/UPENN genomics study

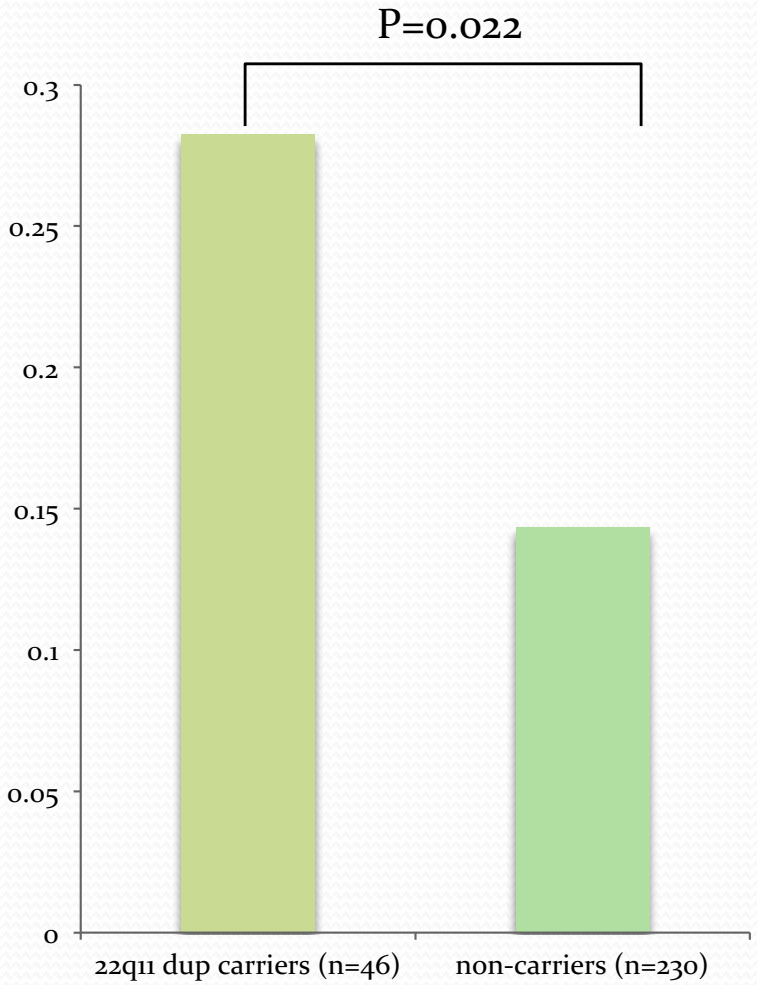
- Recruited from Children's Hospital of Philadelphia (CHOP) (inpatient and outpatient) and 16 primary care clinics in Philadelphia area.
- Recruitment to the Center for Applied Genomics (CAG) biobank is performed by clinical staff who visits the clinics and 16 satellite sites throughout the CHOP network.
- The collection was started in 2006 and continues to bring in ~5-10K new subjects yearly.
- The protocols for recruitment and biobanking are IRB approved, and all subjects provide assent along with consent from at least one parent/guardian.
- Participants presented for diverse medical conditions, ranging from a well child visit and minor problems to chronic condition management to potentially life threatening health problems
  - Not ascertained through psychiatric services
- Ages 0-21 years
- **Non-carriers(5 to 1) for each individual CNV matched for age, gender, ethnicity, mothers education, and zip code**

Selected Neurodevelopmental CNVs

CNV	Assay chr location (hg19) for Taqman	chr location (hg19) for confirmation by Illumina 2.5M chip (size)
MYT1L (dup)	Chr.2:1812929	chr2:1,791,242-2,331,116
NRXN1 (del)	Chr.2:51200453	chr249,921,739-51,032,200
15q13.3 (del/dup)	Chr.15:31485547	chr15:30,620,505-32,520,507
16p11.2 (del/dup)	Chr.16:29989188	chr16:29,581,178-30,181,178
22q11.2 (del/dup)	Chr.22:19938973	chr22:19,000,000-21,500,000

22q11 dup and Perinatal Complications

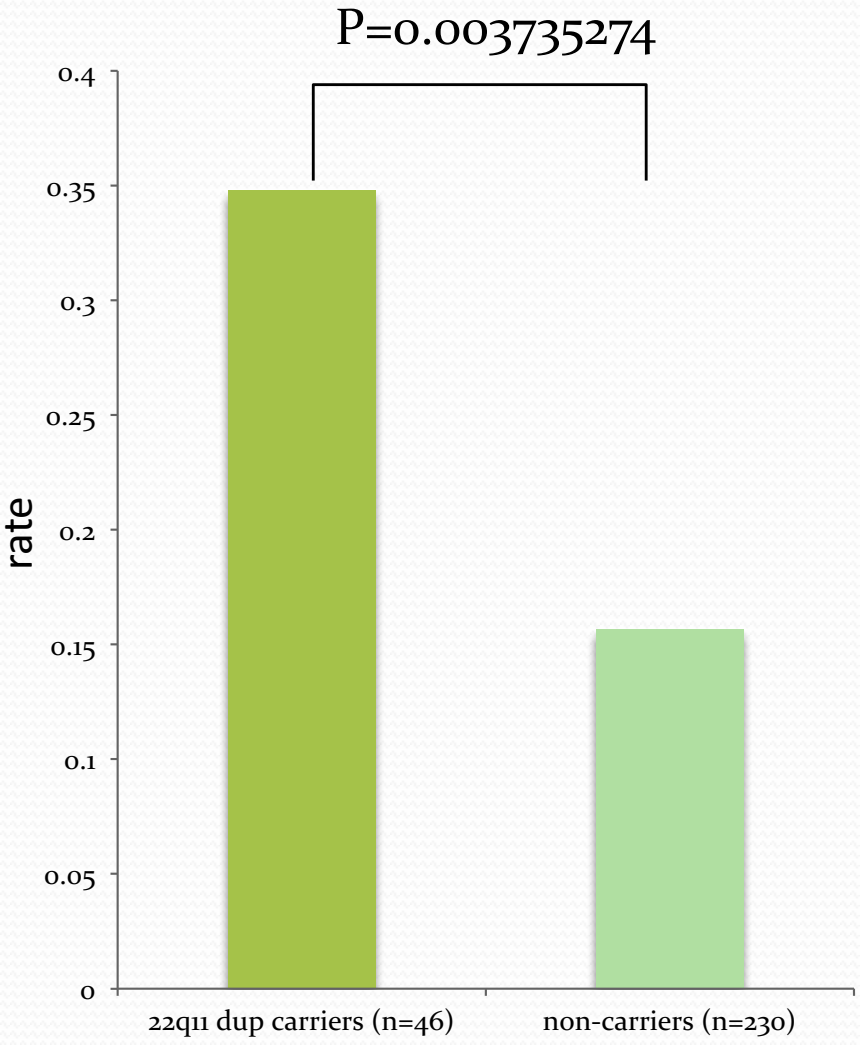
28.3% of 46 carriers



- 774.6(UNSPECIFIED FETAL AND NEONATAL JAUNDICE)
- 765.18(OTHER PRETERM INFANTS, 2,000-2,499 GRAMS),
- 764.97(UNSPECIFIED FETAL GROWTH RETARDATION, 1,750-1,999 GRAMS),774.4(FETAL/NEONATAL HEPATITIS),774.6(FETAL/NEONATAL JAUND NOS)
- 765.03(EXTREME FETAL IMMATURITY, 750-999 GRAMS),765.10(OTHER PRETERM INFANTS, UNSPECIFIED (WEIGHT)),765.10(PREMATURE BIRTH),765.13(OTHER PRETERM INFANTS),765.13(OTHER PRETERM INFANTS, 750-999 GRAMS)
- 766.0(EXCEPTIONALLY LARGE BABY RELATING TO LONG GESTATION),766.0(MACROSOMIA),771.4(UMBILICAL GRANULOMA IN NEWBORN),774.6(JAUNDICE, NEONATAL)
- 772.5(NB ADRENAL HEMORRHAGE)
- 765.10(PREMATURITY),769(RDS (RESPIRATORY DISTRESS SYNDROME IN THE NEWBORN)),779.7(PVL (PERIVENTRICULAR LEUKOMALACIA))
- 770.5(OTHER AND UNSPECIFIED ATELECTASIS OF NEWBORN),770.84(RESPIRATORY FAILURE OF NEWBORN),771.82(URINARY TRACT INFECTION OF NEWBORN),772.4(FETAL AND NEONATAL GASTROINTESTINAL HEMORRHAGE),774.6(UNSPECIFIED FETAL AND NEONATAL JAUNDICE)
- 763.0(Fetus or newborn affected by breech delivery and extraction),773.1(ABO incompatibility affecting fetus or newborn),774.6(Jaundice, neonatal),
- 770.6(TRANSITORY TACHYPNEA OF NEWBORN
- 774.6(Unspecified fetal and neonatal jaundice)
- 764.08(Light-for-dates without mention of fetal malnutrition, 2,000-2,499 grams)

22q11 dup and digestive system

35% of 46 carriers



- 530.81(ESOPHAGEAL REFLUX)
- 558.9(OTHER AND UNSPECIFIED NONINFECTIOUS GASTROENTERITIS AND COLITIS)
- 530.81(ESOPHAGEAL REFLUX)
- 528.00(STOMATITIS AND MUCOSITIS, UNSPECIFIED),528.5(DISEASES OF LIPS),528.9(OTHER AND UNSPECIFIED DISEASES OF THE ORAL SOFT TISSUES),530.7(GASTROESOPHAGEAL LACERATION-HEMORRHAGE SYNDROME)
- 569.3(RECTAL BLEEDING)
- 530.81(ESOPHAGEAL REFLUX)
- 530.10(ESOPHAGITIS, UNSPECIFIED),530.13(EOSINOPHILIC ESOPHAGITIS),530.81(ESOPHAGEAL REFLUX),535.10(ATROPHIC GASTRITIS WITHOUT MENTION OF HEMORRHAGE),535.40(OTHER SPECIFIED GASTRITIS WITHOUT MENTION OF HEMORRHAGE),535.50(GASTRITIS/DUODEN NOS W/O HEMORRH),5
- 530.81(ESOPHAGEAL REFLUX)
- 530.11(REFLUX ESOPHAGITIS),530.81(ESOPHAGEAL REFLUX), 536.3(GASTROPARESIS),
- 530.81(ESOPHAGEAL REFLUX),530.81(GERD (GASTROESOPHAGEAL REFLUX DISEASE))
- 560.0(INTUSSUSCEPTION)
- 530.81(ESOPHAGEAL REFLUX)
- 530.11(REFLUX ESOPHAGITIS),530.81(ESOPHAGEAL REFLUX)
- 530.81(ESOPHAGEAL REFLUX),530.81(GERD (GASTROESOPHAGEAL REFLUX DISEASE)),558.3(ALLERGIC GASTROENTERITIS AND COLITIS)
- 530.81(GERD (gastroesophageal reflux disease)),530.81K(NO DX NAME PROVIDED)

Gastroesophageal Reflux Disease (GERD) in childhood

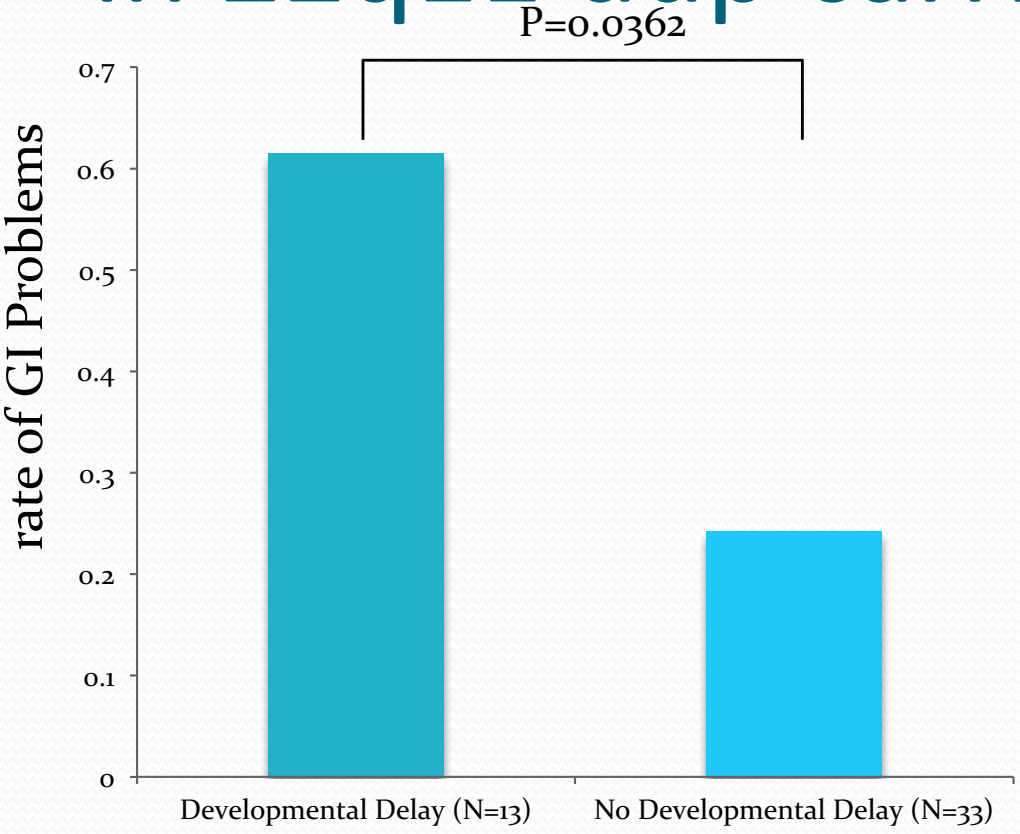
(Fonkalsrud & Ament, 1996)

- Disorder is a complex with significant symptoms, such as failure to thrive, secondary respiratory disease and/or esophageal damage
- Associated with neurologic disorders
- Physiological studies indicate a high prevalence of autonomic neuropathy (lower esophageal passage, lower esophageal sphincter tone
- May reflect a developmental disorder of the parasympathetic nervous system (vagus nerve)

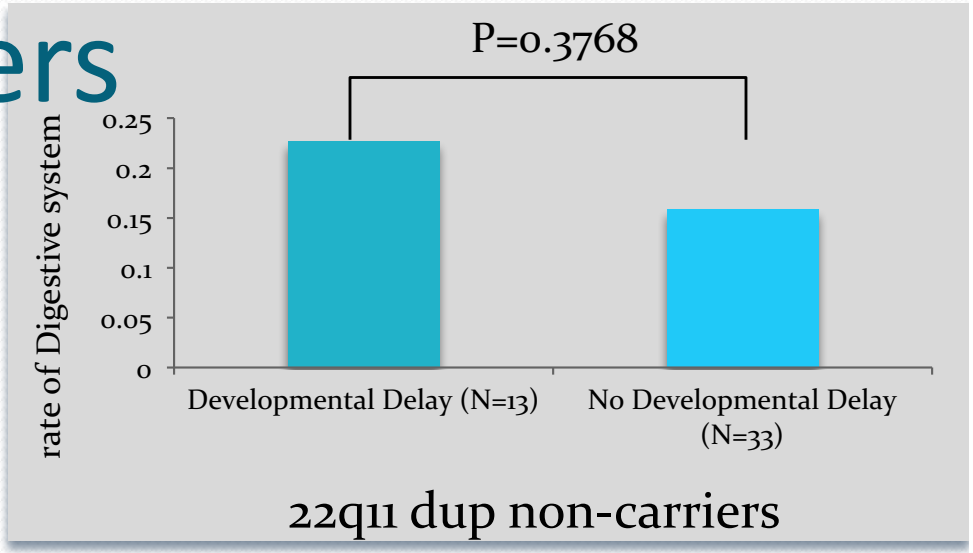
Developmental delay and GI problems

22q11 dup carriers

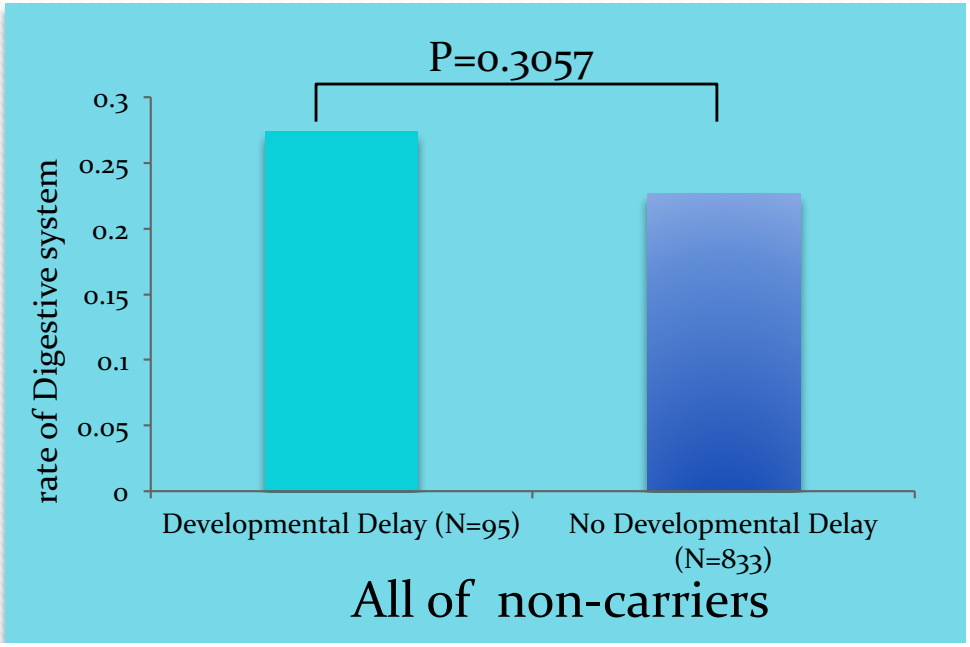
in 22q11 dup carriers



Non carriers have no relation between developmental delay and GERD



22q11 dup non-carriers



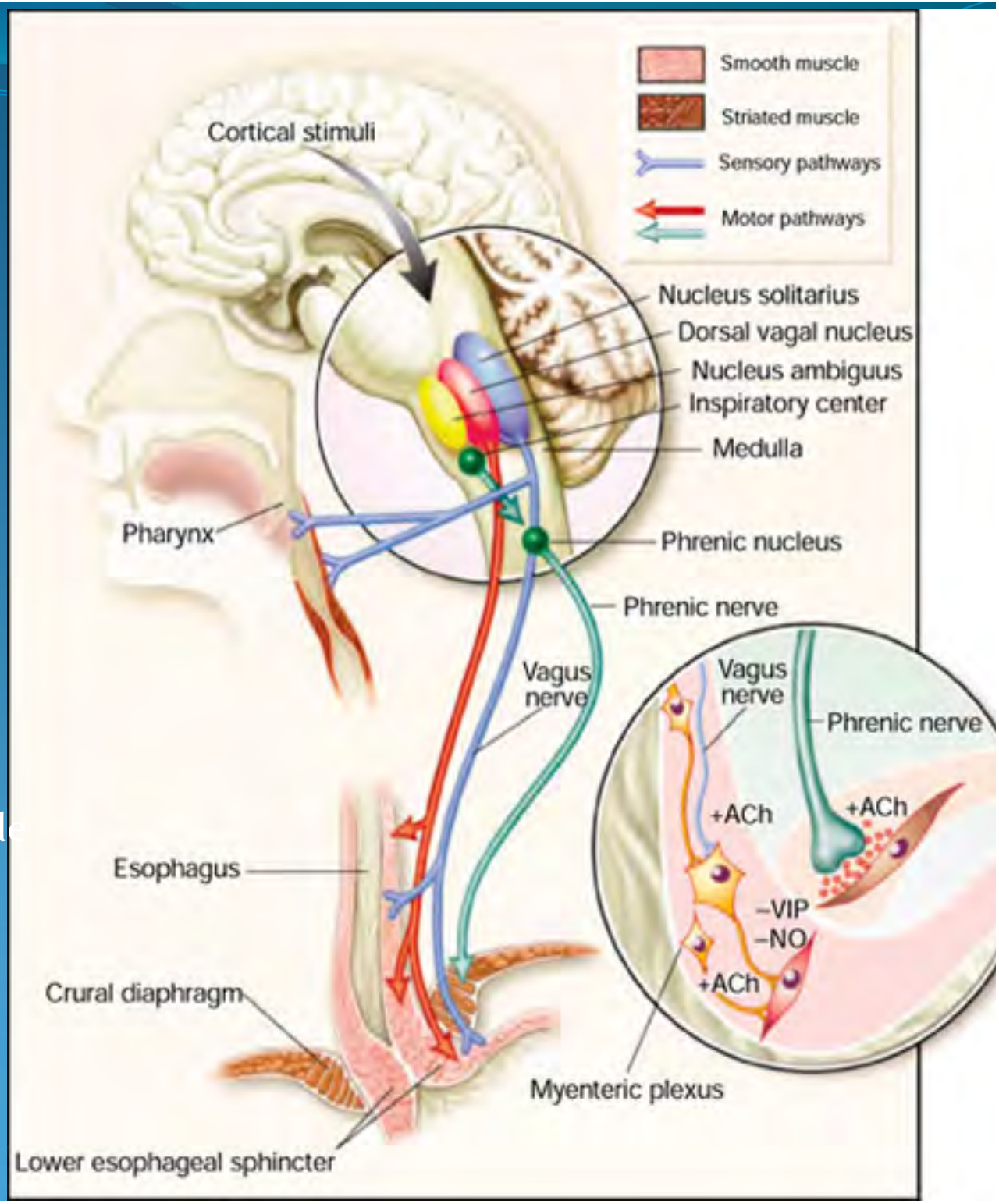
All of non-carriers

Innervation of the Lower Gastroesphogeal Sphincter

Note multiple hormone:
Gastrin, motilin, substance P
Keep LES tone high

Cholecystokinin, secretin, Glucagon, VIP and NO
Relax the sphincter.

Physiological subtypes include
Lower LES tone
More frequent LESRs

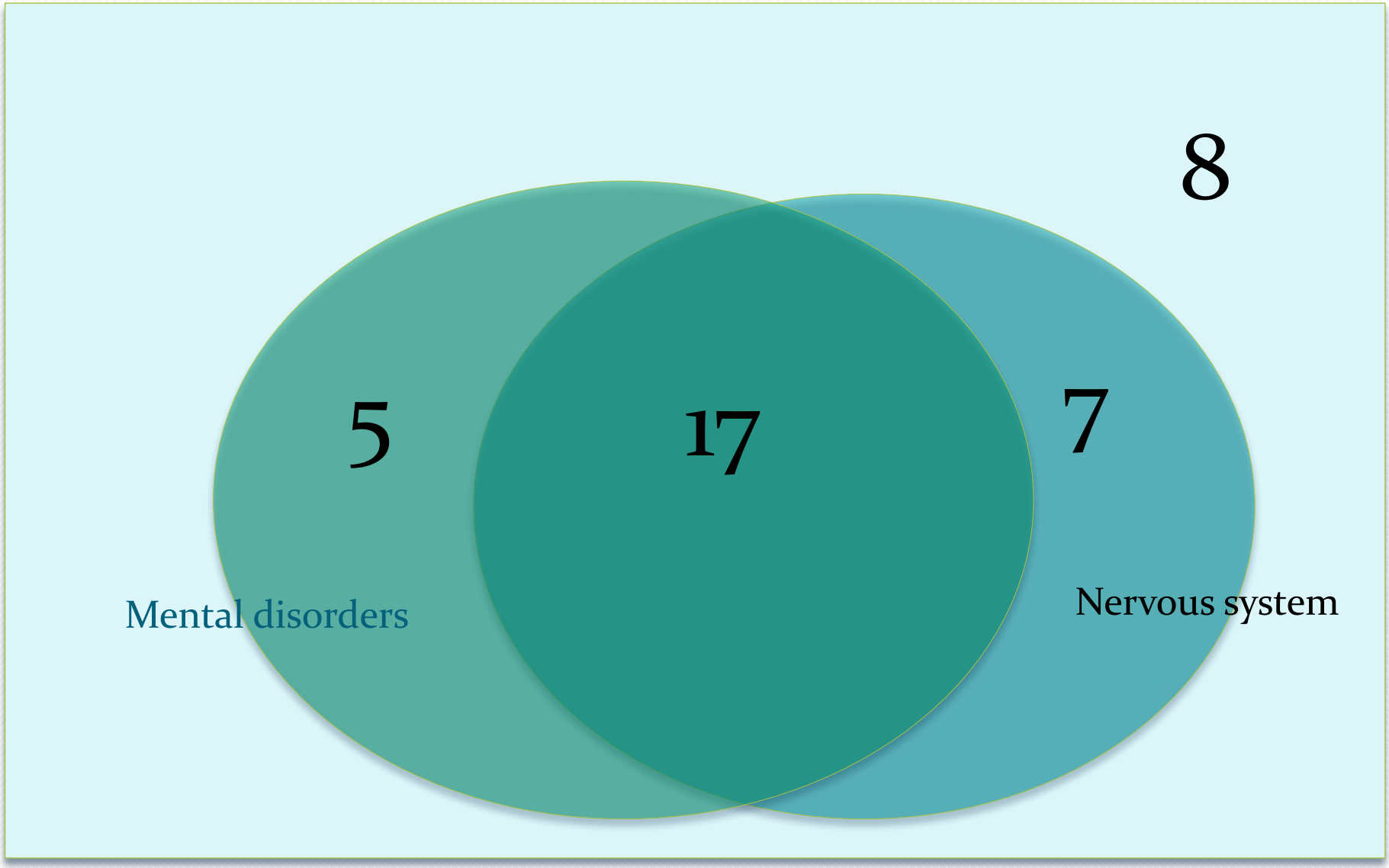


Gastroesophageal Reflux Disease (GERD) in childhood

(Fonkalsrud & Ament, 1996)

- Disorder is a complex with significant symptoms, such as failure to thrive, secondary respiratory disease and/or esophageal damage
- Associated with neurologic disorders
- Physiological studies indicate a high prevalence of autonomic neuropathy (lower esophageal passage, lower esophageal sphincter tone
- **In 22q11 dup may reflect a developmental disorder of the parasympathetic nervous system (vagus nerve**)

16p11 del: mental/neurodevelopmental and/or nervous system (37 carriers)



Preliminary Findings: CHOP study

- Replication of 22q11 dup and 16p11 deletion syndromes
- Unexpected prominence for GERD for 22q11 dup.(First DNV for digestive disorder) or possible "vagal nerve developmental disorder".
- High predicted rates of mental/developmental disorders for 15q13 del
- Unexpected lack of disease association for NRXN deletion/ or MYT1L (NRXN assoc. for caucasians)
- Significant "mental disorders"association based on pediatric records alone (in person follow up being attempted) predict higher broad Dx rate
- Would a future birth cohort poulation study be feasible?

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- THANK YOU!